

35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1, 4, 9, and 11-14 under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claim 1 is rejected because of an improper Markush group. Applicants have amended the Markush group, as suggested by the Examiner.

Claim 4, is rejected because the claim has multiple uses of the term "polypeptide". Applicants have replaced the second occurrence of "polypeptide" with "linker" as suggested by the Examiner

Applicants submit that the claims 1, 4, and the dependent claims therefrom, as amended, are clear and the rejection is moot.

35 U.S.C. § 103

The Examiner maintained the rejection of claims 1, 5 and 10-14 under 35 U.S.C. § 103(a) as being unpatentable over Pastan *et al.* (U.S. Patent 5,635,599) in view of Lin (U.S. Patent 4,703,008). The Examiner argues that it would have been obvious to make circular permuted EPO molecules having a breakpoint at positions 25, 27, 30, 32, 80, 82, 88, 116, or 121.

In the telephone interview with the Examiner the issue of the enablement of the cited references was discussed. The Examiner agreed to review the federal circuit decision related to '008 and review the '599 file history.

Applicants maintain the arguments in traverse of this rejection, set forth in the response dated 09 February 1999, that the Examiner has failed to establish a *prima facie* case of obviousness.

Applicants argued that '008 does not teach individual sites at which amino acid substitutions can be made. In response, the Examiner states:

"Lin discloses at column 11 that synthetic sequences that are partially duplicative of any of the two naturally occurring sequences could be made that retain activity." (page 7, lines 13-15 of Paper No.9)

However, since under the obviousness standard prior art is required to teach, then the prior art can only be applied to the extent that the disclosure is enabling. The District Court, in *In re Amgen* (13 USPQ2d 1737, 1989) and the Federal Circuit Court of Appeals in *In re Amgen* (18 USPQ2d 1610, 1991) has ruled that the '008 disclosure is not enabling for EPO analogs. The Federal Circuit Court of Appeals stated:

"Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This 'disclosure' might well be justify a generic claim encompassing these and similar analogs, but

it represents inadequate support for Amgen's desire to claim all EPO gene analogs. (emphasis added) (In re Amgen (18 USPQ2d, 1991, column 1, page 1027)

Therefore, '008 can only be relied upon as prior art for what the Federal Circuit court has determined the disclosure enables. As clearly established by the Federal Circuit Court of Appeals, '008 only enables the sequences of human and monkey EPO, **not analogs** thereof. Consequently, '008 can **not** be relied upon to teach that amino acid substitutions can be made at the positions at which human and murine EPO differ. Therefore, '008, does not reasonably suggest breakpoints at positions 25, 27, 30, 32, 80, 82, 88, 116, or 121 for circular permutation.

Applicants argued that at best, '599:

(a) is limited to the teaching of only two circular permutation breakpoints (37-38 and 104-105) of IL-4 in the context of a chimeric molecules with a cytotoxin or an antibody fragment (Fv);

(b) only one circularly permuted form each of IL-2 (Example 5, column 25-26), G-CSF (Example 6, column 26) and GM-CSF (Example 6, column 26) are disclosed in '599; and it is **not** shown that these IL-2, G-CSF, and GM-CSF molecules have any activity.

(c) as admitted by the Examiner, '599 does **not** disclose a working example of circular permutation of Erythropoietin

(d) the totality of the prior art provides only a very limited number of examples of circular permuted proteins and

the results have been variable and there is a great deal of unpredictability associated with circular permutation.

(e) the generic speculation in '599 about some general considerations for selecting breakpoints are not supported by the '599 specification.

The Examiner counter-argued that the applicant's interpretation of '599 was too narrow as evidenced by the patented claims that are directed to fusion proteins comprising a circular permutation of IL-4, IL-2, G-CSF and GM-CSF.

Once again, since under the obviousness standard prior art is required to teach, then the prior art can only be applied to the extent that the disclosure is enabling.

The file history of '599 reveals that claim 18 in the original application claims a fusion protein comprising a circularly permuted ligand. Applicants have summarized the course of events in the file history below:

(1) The Examiner (the same as in the present application), rejected claim 18 under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling **only** for claims limited to fusion proteins wherein IL-4 is the ligand (page 5 of Paper No. 6 of '008 dated 04/04/95).

(2) In response to the 112, first paragraph, rejection the Applicants amended claim 18 to recite that the ligand is selected from the group consisting of GM-CSF, G-CSF, IL-4 and IL-2 (Paper No. 8, dated 08/04/95).

(3) The Examiner maintained the 112, first paragraph, in the FINAL rejection of claim 18 (Paper No. 9, dated 11/13/95). The Examiner argued:

- (a) the art was unpredictable; and
- (b) the specification provides limited guidance regarding suitable opening sites in IL-4, IL-2, GM-CSF and G-CSF.

(4) The applicants filed a response under 37 C.F.R. § 1.116 amending claim 18 to recite only IL-4 and adding new claims reciting IL-2, G-CSF and GM-CSF in separate independent claims (Paper No. 11, dated 03/20/96).

(5) The Examiner maintained the rejection in the Advisory Action (Paper No. 12, dated 04/25/96).

(6) The Examiner was persuaded by the applicants arguments that the specification was enabling for IL-4 permuteins in an Examiners Interview (Paper No. 15, dated 05/08/96).

(7) The Examiner proposed an Examiner's amendment, which was accepted by the Applicants and entered as part of the Notice of Allowance, with claims directed to cytotoxic fusion proteins comprising IL-2, IL-4, G-CSF and GM-CSF.

At best, the file history clearly establishes that the specification is limited, as to the scope of its enablement, which is directed to cytotoxic fusion proteins comprising IL-2, IL-4, G-CSF and GM-CSF. Therefore, '599 can only be relied upon as prior art for what the file history has established the disclosure enables. As clearly indicated from the file history, '599 only enables circular permutation of IL-2, IL-4, G-CSF and GM-CSF. Consequently,

'599 can not be relied upon to teach the circular permutation of Erythropoietin.

Pastan, '599, is at best an invitation for experimentation not a basis for establishing a *prima facie* case of obviousness. It can not be concluded, from the limited disclosure and general speculation presented by Pastan about what may or may not be a good candidate for opening sites for other molecules beyond the scope of what is claimed. The general guideline that sites at which substitutions can be made are good opening sites for circular permutation is only unsubstantiated speculation. The '008 specification does teach where to make opening sites because it is only enabled for the two disclosed molecules.

In conclusion, the applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because the scope of the enablement of '008 is limited to the two species disclosed and the '599 specification is not enabled beyond the scope of the claimed molecules. Therefore, it has **not** been established that the prior art suggests the presently claimed molecules and the prior art does not provide a reasonable expectation of success. The applicants submit that the rejection is moot.

35 U.S.C. § 103

The Examiner introduced a new rejection of claims 1-4 and 6-9 under 35 U.S.C. § 103(a) as being unpatentable over Pastan *et al.* (U.S. Patent 5,635,599) in view of Lin (U.S.

Patent 4,703,008) and further in view of Chaudhary et al. (1989, *Nature* 339:394-397) and Cousens et al. (U.S. Patent 4,751,180). The Examiner states that '599 and '008 do not teach the GlySer rich linker required by claims 2-4 and 6-9. The Examiner argues that it would have been obvious to use the GlySer-rich linker for connecting antibody variable domains, as disclosed by Chaudhary and that non-polar amino acids are useful for a flexible linker, as disclosed by Cousens.

For the same reasons set forth above regarding '008 and '599, applicants submit that the rejection is moot. In respect to the new references, applicants argue that the linkers of Chaudhary et al. and Gearing et al. ('180) are in the context of fusion proteins and the requirements of linkers for joining fusion proteins are different from the requirements of the linkers for joining the ends of circular permuted molecules. In '180 the function of the "hinge" is defined as to:

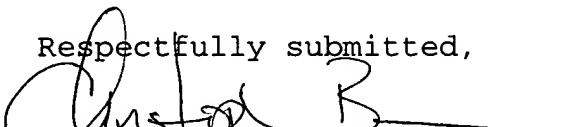
" . . . separate further the two fused polypeptides. Such a "hinge" would allow for steric flexibility so that the fused polypeptides would be less likely to interfere with each other, thus preventing incorrect folding . . ." (column 4, lines 17-21).

Clearly, the purpose of the linker in the presently claimed molecules is not to separate the amino acid sequences on either side of the linker to avoid interference with to prevent incorrect protein folding, but rather the function is properly position the sequences to allow them to interact so that the resulting amino acid can properly fold. It is also apparent that the authors of '599 were also cognoscente

of the distinct functions between such, as evidenced by separate definitions for "spacer" (column 3 lines 54-61) and "linker" (column 4 lines 7-18).

Claims 1-22 are pending and claims 15-22 are withdrawn from consideration. Reexamination and reconsideration of the application as amended are requested. In view of the above, it is submitted that the elected claims 1-14 are in condition for allowance. Allowance of the pending claims at an early date is solicited.

Respectfully submitted,



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